

Sulfonamides and Sulfonamide Combinations*

Overview

Due to low cost and relative efficacy against many common bacterial infections, sulfonamides and sulfonamide combinations with diaminopyrimidines are some of the most common antibacterial agents utilized in veterinary medicine. The sulfonamides are derived from sulfanilamide. These chemicals are structural analogues of p-aminobenzoic acid (PABA). All sulfonamides are characterized by the same chemical nucleus. Functional groups are added to the amino group or substitutions made on the amino group to facilitate varying chemical, physical and pharmacologic properties and antibacterial spectra. Most sulfonamides are too alkaline for routine parenteral use. Therefore the drug is most commonly administered orally except in life threatening systemic infections. However, sulfonamide preparations can be administered orally, intramuscularly, intravenously, intraperitoneally, intrauterally and topically.

Sulfonamides are effective against Gram-positive and Gram-negative bacteria. Some protozoa, such as coccidians, *Toxoplasma* species and plasmodia, are generally sensitive. Chlamydia, *Nocardia* and *Actinomyces* species are also sensitive. Veterinary diseases commonly treated by sulfonamides are actinobacillosis, coccidioidosis, mastitis, metritis, colibacillosis, pododermatitis, polyarthritis, respiratory infections and toxoplasmosis. Strains of rickettsiae, *Pseudomonas*, *Klebsiella*, *Proteus*, *Clostridium* and *Leptospira* species are often highly resistant.

Sulfonamides are bacteriostatic antimicrobials and are most effective in early stages of acute infections when organisms multiply rapidly. Intact immunity is required for effectiveness. Bacteria utilize PABA to initiate folic acid synthesis. Sulfonamides competitively inhibit enzymes that function in synthesis of folic acid, which is required for production of purine, thymidine, methionine, glycine and formylmethionyl-transfer RNA. The end result is inhibition of protein synthesis, metabolism and growth. Often a lag in effectiveness is observed early in the course of therapy. This lag period is explained by cellular use of existing stores of folic acid or folic acid end products.

Sulfonamides are categorized in veterinary medicine as standard use, highly soluble, poorly soluble, potentiated and topical sulfonamides. In human medicine sulfonamides are characterized as short, medium and long-acting. The human classification does not apply in veterinary medicine due to species differences in metabolism and excretion.

Examples of standard use sulfonamides are sulfathiazole, sulfamethazine (sulfadimidine), sulfamerazine, sulfadiazine, sulfapyridine, sulfabromomethazine, sulfaethoxypyridazine, sulfamethoxypyridazine, sulfadimethoxine and sulfachlorpyridazine. These drugs are used to treat systemic infections caused by susceptible organisms.

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Highly soluble sulfonamides are utilized primarily in therapy for urinary tract infections, due to rapid urinary excretion in mostly unchanged form. Examples of these highly water soluble antimicrobials are sulfisoxazole (sulfafurazole) and sulfasomidine.

Poorly soluble sulfonamides are also used to combat urinary tract infections and are utilized in the treatment of ulcerative colitis in dogs. This is the only group of sulfonamides that is not rapidly absorbed from the gut. The lack of water solubility prevents absorption from the gastrointestinal tract. Phthalylsulfathiazole and succinylsulfathiazole are hydrolyzed in the lower gastrointestinal tract and sulfathiazole, the active agent, is released. Salicylazosulfapyridine is also hydrolyzed in the gut and sulfapyridine and 5-aminosalicylic acid (an anti-inflammatory agent), are released.

Potentiated sulfonamides include sulfa/pyrimethamine and sulfa/trimethoprim combinations. Trimethoprim/sulfamethoxazole (TMP-SMX) combinations were introduced in the United States in 1974, but the drugs were already widely used in combination. TMP-SMX is now one of the most cost effective, widely used antimicrobials in the world. Pyrimethamine and trimethoprim also block tetrahydrofolate synthesis (folic acid synthesis). In fact in combination with sulfonamides they sequentially inhibit two enzymes necessary for synthesis of folic acid. These combination drugs are used to treat both bacterial and protozoal infections. Potentiated sulfonamides exhibit bactericidal activity against many aerobic Gram-positive and Gram-negative bacteria. They are effective against strains of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Proteus mirabilis*, *E. coli*, *Salmonella* species, *Klebsiella pneumoniae*, *Pseudomonas cepacia*, *Pseudomonas pseudomallei*, *Aeromonas hydrophila*, *Yersinia enterocolitica*, *Vibrio cholerae*, *Neisseria gonorrhoeae*, *Nocardia asteroides*, *Listeria monocytogenes*, *Pneumocystis jirovecii*, *Pneumocystis carinii*, *Isospora* and *Cyclospora* species. They are also effective against some nosocomial infections important in human medicine, such as *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and *Serratia marcescens*. TMP-SMX, however, is ineffective against *Pseudomonas aeruginosa* and *Bacteroides* species. Due to the rapid increase in resistant strains, the drug is no longer appropriate for treatment of shigellosis. In human medicine TMP-SMX is ideal for oral therapy because over ninety percent is absorbed when administered orally. TMP-SMX is utilized in human medicine as oral therapy for treatment of infections caused by methicillin sensitive *Staphylococcus aureus* and infections caused by Gram-negative bacteria. TMP-SMX is often utilized in therapy for traveler's diarrhea due to enterotoxigenic *E. coli* and, when antibiotic therapy is necessary, is used to treat cat scratch disease. The drug is also used to treat mild to moderate infections caused by community acquired methicillin resistant *Staphylococcus aureus* and is widely used in therapy for urinary tract infections when the infection is caused by Gram-negative bacteria, although in some parts of the United States resistance is now detected in eighteen percent of the pathogens cultured from women with acute cystitis. TMP-SMX is often employed as a prophylactic drug in the prevention of recurrent urinary tract infections. TMP-SMX can be combined with clindamycin for therapy of infected human and animal bites and with erythromycin or alone (in adults) as an alternate therapy for sinusitis or otitis media.

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Topical sulfonamides include ophthalmic preparations, such as sulfacetamide and wound and burn preparations, such as mafenide, silver sulfadiazine and sulfathiazole. These preparations are used to combat both Gram-positive and Gram-negative organisms.

In human medicine sulfisoxazole, SMX, sulfadiazine and sulfamethizole are considered short acting sulfonamides. Sulfadoxine is an example of a long acting agent.

A common mechanism of resistance to sulfonamides is overproduction of PABA or altered dihydropteroate synthetase, one of the enzymes utilized in folic acid synthesis. This mode of resistance is primarily plasmid mediated and cross resistance is common. *E. coli*, *Staphylococcus aureus* and *Neisseria* species are the bacteria most likely to acquire this mode of resistance. Chromosomally mediated resistance due to alteration of dihydropteroate synthetase also occurs. Resistance is slow to emerge but is widespread in many animal and human populations. Resistance to sulfonamides in human medicine has severely restricted clinical usefulness.

Bacterial resistance to potentiated sulfonamides, like TMP-SMX, is increasing and, therefore, diminishing the effectiveness of the combination agent. Resistance occurs through several mechanisms. Decreased permeability, efflux pumps and alterations in target enzymes, such as mutations in dihydrofolate reductase, all occur. Along with excessive macrolide use, TMP-SMX overuse is responsible for most multi-drug resistant *Streptococcus pneumoniae* and has led to problems with penicillin and methicillin resistant *S. pneumoniae*; therefore use of TMP-SMX should be avoided in respiratory infections. High rates of resistance in *Haemophilus influenzae* also have been discovered. Resistance to both TMP and SMX can be transferred between bacteria.

In general sulfonamides are well distributed in all body tissues, especially prostatic fluid. These drugs are also passively diffused to milk and although levels are usually inadequate to control infection, sulfonamide residues may be detected. TMP-SMX is also distributed well throughout the body. High concentrations of both components can be found in bile, CSF, prostatic fluid and sputum. Sulfonamides are metabolized in the liver but are primarily excreted unchanged in the urine. There are exceptions, however. A large proportion of SMX is metabolized by the liver and only thirty percent is excreted unchanged by the kidneys. Due to urinary excretion, if solubility levels are exceeded, crystals may precipitate. The chance of crystal formation can be reduced by alkalinizing the urine, reducing doses in the presence of renal insufficiency and increasing fluid uptake. Utilization of potentiated sulfonamides like TMP-SMX or triple sulfonamide preparations also reduces the potential for crystal formation.

Occasionally severe side effects are observed with sulfonamides and potentiated sulfonamides. The sulfonamides can cause hepatic necrosis, serum sickness like syndrome, acute hemolytic anemia, agranulocytosis and Stevens-Johnson syndrome. TMP can cause leukopenia, thrombocytopenia, granulocytopenia and pseudomembranous colitis; the combination drug, TMP-SMX, can cause all forms of hemolytic reactions, but the incidence is very low. Hypersensitivity to TMP-SMX is very common. There are

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concerns with TMP-SMX administration in pregnancy centers on the antifolate mechanisms and possible risk of neural tube defects. Sulfonamide competition for bilirubin binding sites may also increase risk of kernicterus. Therefore these drugs should only be used in pregnancy if the potential benefit justifies the potential risk to the fetus (pregnancy category C). The same concerns are expressed when TMP-SMX is administered to nursing mothers.

***References available by request. Call the Infectious Disease Epidemiology Section, Office of Public Health, Louisiana Department of Health and Hospitals (504-219-4563)**